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First stereoselective total synthesis of paecilomycin G

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reaction.

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ABSTRACT

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Introduction

Resorcylic acid lactones (RALs)¹ are an important subgroup of polyketide natural products which possess interesting structural features and exhibit a wide variety of bioactivities such as cytotoxic,^{2,6a} antiviral, antiparasitic,³ antiplasmodial,⁴ nematicidal,⁵ antibacterial, antifouling,⁶ antimalarial,^{2b} protein tyrosine kinase, and ATPase inhibition.⁷ In 2012, Wei and co-workers isolated three new RALs, paecilomycin G-I $(1-3)^8$ along with eight other known RALs, aigialomycins B–D (**4–6**),^{2b} 1',2'-epoxy aigialomycin D (**7**),^{2d} zearalenone (**8**),⁹ 7'-dehydro zearalenone (**9**),¹⁰ trans-7',8'-dehydrozearalenol (10),¹¹ and LL-Z1640-1 (11)¹² from the mycelia solid culture of Paecilomyces sp. SC0924 (Fig. 1). Their structures were elucidated by spectroscopic methods and chemical means. Antifungal activities of these lactones were evaluated using Peronophythora litchii as the test microorganism. Although, various paecilomycins have been synthesized,¹³ to the best of our knowledge there are no reports on the synthesis of paecilomycin G(1). The interesting biological profiles of these classes of compounds and our interest in the synthesis of macrolides¹⁴ prompted us to take up the synthesis of paecilomycin G(1) in a convergent manner by employing the Sharpless asymmetric dihydroxylation, Jacobsen hydrolytic kinetic resolution, Corey-Fuchs reaction, Stille coupling, Mitsunobu reaction, and RCM reaction as the key steps starting

http://dx.doi.org/10.1016/j.tetlet.2016.05.046 0040-4039/© 2016 Elsevier Ltd. All rights reserved. from commercially available 1,4-buatne diol and 2,4,6-trihydroxybenzoic acid.

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Results and discussion

The stereoselective total synthesis of resorcylic acid lactone, paecilomycin G(1) has been accomplished.

The key steps involved are the Corey-Fuchs reaction, Sharpless asymmetric dihydroxylation, Jacobsen

hydrolytic kinetic resolution, Stille coupling, Mitsunobu reaction, and Ring-closing metathesis (RCM)

The retrosynthetic analysis of paecilomycin G (1) is depicted in Scheme 1. The macrolactone 1 was envisaged from bis-alkene 12 by utilizing RCM protocol. Bis-alkene 12 was planned from coupling of compound 13 and 14 under Mitsunobu esterification conditions. Wherein, fragment 13 could be obtained from commercially available 2,4,6-trihydroxybenzoic acid 15 and fragment 14 could be obtained from compounds 16 and 17. Further, compound 16 may be prepared from easily available 1,4-butane diol 18, an easily available starting material.

The chiral secondary alcohol **14** was synthesized as shown in Scheme 2 starting from 1,4-butane diol. Accordingly, the 1,4-butane diol **18** was selectively mono protected as its benzyl ether using BnBr, NaH in THF to afford **19** in 80% yield. Oxidation of the alcohol was achieved under the Swern oxidation condition $\{(COCI)_2, DMSO, TEA, CH_2CI_2, -78 \,^{\circ}C\}$ to afford the corresponding aldehyde which was further treated with (ethoxycarbonyl-methylene)triphenylphosphorane for two carbon homologations in benzene under reflux conditions to provide (*E*)-allyl ester **20** in 91% yield for two steps. The *E*-geometry of the double bond was confirmed by the coupling constant between the respective olefin protons (*J* = 15.6 Hz). Subsequent partial reduction of the ester present in **20** to an aldehyde was achieved using DIBAL-H, then it was treated with CBr₄ and PPh₃ to furnish dibromo olefin

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Figure 1. Representative examples of resorcylic acid lactones.

which upon treatment with *n*-BuLi gave alkyne **16** in 82% yield.¹⁵ Regioselective opening of the epoxide **17** (prepared from racemic propylene oxide which was resolved by using (*R*,*R*)-Salen-Co^{III}OAc catalyst¹⁶) was achieved with lithiated alkyne **16** to afford homo propargyl alcohol **21** in 84% yield. The secondary alcohol present in **21** was protected as its TBS ether using TBSCl/imidazole in CH₂Cl₂ to furnish **22** in 94% yield. Then, compound **22** was treated under the Sharpless asymmetric dihydroxylation conditions¹⁷ using Ad-mix- α to provide diol **23** in 82% yield with good diastere-oselectivity (>97%, based on HPLC), which was then treated with



Scheme 1. Retrosynthetic analysis of compound 1

2,2-dimethoxypropane in the presence of a catalytic amount of PPTS to afford **24** in 87% yield. Compound **24** was then subjected to Raney-Ni under hydrogen atmosphere for alkyne reduction as well as benzyl deprotection in one pot to obtain compound **25**. The primary alcohol **25** was efficiently oxidized with IBX in DMSO/THF at ambient temperature to provide the corresponding aldehyde followed by the addition to a one-carbon ylide (generated from $CH_3PPh_3^{+}I^-$, K^tOBu in THF) led to olefin **26** in 76% yield. Desilylation of **26** using TBAF in THF gave the desired alcohol fragment **14** in 89% yield.

Now the requisite acid fragment **13** was taken up and was prepared from commercially available 2,4,6-trihyroxybenzoic acid monohydrate **15** in five steps (Scheme 3). Treatment of compound **15** with trifluoroacetic acid (TFA), trifluoroacetic anhydride (TFAA), and acetone provided the acetonide protected compound **27** in 60% yield.¹⁸ Then, selective protection of the 4-hydroxyl group in **27** was achieved under the Mitsunobu conditions (PPh₃ and DIAD)¹⁹ which was subsequently treated with trifluoromethanesulfonic anhydride and pyridine in CH₂Cl₂ to furnish the corresponding triflate **29** in 96% yield. Then, triflate **28** was subjected to the Stille coupling²⁰ with vinyltributyltin in the presence of LiCl to afford **30** in 88% yield. The isopropylidene protection was removed using LiOH·H₂O in THF/H₂O (2:1) to afford the desired aromatic acid **13** in 87% yield.

With both alcohols **13** and **14** in hand, we proceeded for the construction of the macrocyclic framework (Scheme 4). The esterification reaction between **13** and **14** was carried out under the Mitsunobu reaction conditions to obtain the desired ester **12** in 84% yield. Then, ester **12** was treated with 10 mol% of the Hoveyda–Grubbs second generation catalyst in degassed toluene to provide the required lactone **31** in 86% yield and with exclusive *E*-selectivity. Removal of the acetonide functionality in **31** was achieved by treatment with 2 N HCl to furnish the target molecule²¹ in 93% yield.

The spectral data (¹H, ¹³C, MS and IR) of the synthesized target compound were in good agreement with reported values of the natural product **1** (see Supporting information for comparison table), but when the specific rotation of synthetic **1** was compared surprisingly, it was comparable with the specific rotation given to



Scheme 2. Reagents and conditions: (a) NaH, BnBr, THF, 0 °C-rt, 4 h, 80%, (b) (1) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C; (2) Ph₃P = CHCO₂Et, benzene, reflux, 4 h, 91% from two steps; (c) (1) DIBAL-H, toluene, -78 °C, 30 min; (2) PPh₃, CBr₄, 0 °C, 1 h; (3) *n*-BuLi, -78 °C, 1 h, 82% over three steps; (d) *n*-BuLi, BF₃·Et₂O, **17**, THF, -78 °C, 4 h, 84%; (e) TBSCl, imidazole, CH₂Cl₂, 0 °C-rt, 6 h, 94%; (f) AD-mix- α , MeSO₂NH₂, *t*-BuOH/H₂O, 0 °C, 24 h, 82%; (g) 2,2-DMP, PPTS (cat.), CH₂Cl₂, 0 °C-rt, 10 h, 87%; (h) Raney-Ni, H₂, EtOH, 12 h, 95%; (i) (1) IBX, DMSO/THF, rt; (2) CH₃PPh₃¹⁻, K^tOBu, 0 °C-rt, 2 h, 89%.

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Scheme 3. Reagents and conditions: (a) TFA, TFAA, acetone, 0 °C-rt, 48 h, 60%; (b) PPh₃, DIAD, MeOH, THF, 0 °C-rt, 3 h, 88%; (c) Tf₂O, pyridine, CH₂Cl₂, 0 °C-rt, 4 h, 96%; (d) vinyltributyltin, LiCl, Pd(PPh₃)₄, DMF, 60 °C, 6 h, 88%; (e) LiOH H₂O, THF/ H₂O (2:1), 0 °C-rt, 24 h, 87%.



Scheme 4. Reagents and conditions: (a) PPh₃, DIAD, toluene, 0 °C-rt, 30 min, 84%; (b) Hoveyda-Grubbs second generation catalyst (10 mol %), toluene, 80 °C, 4 h, 86%; (c) 2 N HCl/THF (1:1), 6 h, rt, 93%.

paecilomycin I. {synthetic **1** specific rotation $[\alpha]_D^{27}$ –111.3 (*c* 0.40, MeOH) where as natural **1** $[\alpha]_D^{20}$ –0.50 (*c* 0.40, MeOH) and paecilomycin I $[\alpha]_{D}^{20}$ –106.67 (*c* 0.24, MeOH)}. As all the stereogenic centers were generated using well established protocols, specific rotation value of the natural product needs to be reconsidered.

In conclusion, we have demonstrated the first stereoselective total synthesis of paecilomycin G(1) by employing the Corey-Fuchs reaction, Sharpless asymmetric dihydroxylation, Jacobsen hydrolytic kinetic resolution, Stille coupling, Mitsunobu reaction and RCM as the key reactions in 13 longest linear steps with an overall yield of 14.5% starting from 18. Synthetic studies toward structurally related RALs along with their analogs are still under investigation in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05. 046.

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- Paecilomycin G (1): Mp = 163–166 °C. $[\alpha]_D^{27}$ –111.3 (c 0.40, MeOH); IR (KBr): 3307, 2936, 2861, 1643, 1606, 1574, 1461, 1384, 1355, 1317, 1256, 1209, 1158, 1111, 1036, 993 cm⁻¹; ¹H NMR (500 MHz, pyridine-*d*₅): δ 12.76 (br s, 1H), 7.20 (d, J = 14.6 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 6.65 (d, J = 2.6 Hz, 1H), 5.86 (ddd, J = 14.3, 10.2, 3.8 Hz, 1H), 5.00-4.94 (m, 1H), 4.06 (br d, J = 9.7 Hz, 1H), 3.98 (br d, J = 10.7 Hz, 1H), 3.72 (s, 3H), 2.43–2.27 (m, 4H), 1.99–1.91 (m, 1H), 1.87–1.80 (m, 1H), 1.72–1.64 (m, 1H), 1.51–1.37 (m, 3H), 1.28 (d, J = 6.1 Hz, 3H); ¹³C NMR (125 MHz, pyridine-d₅): δ 172.09, 166.28, 164.55, 144.13, 134.20, 132.51, 108.82, 104.44, 100.73, 74.32, 68.26, 67.70, 55.52, 35.34, 32.86, 32.71, 29.95, 21.48, 21.01; MS (ESI): $m/z = 373 (M+Na)^+$; HRMS (ESI): calcd for $C_{19}H_{26}O_6Na$ (M+Na)⁺ 373.1621, found 373.1632.